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Fibromyalgia, Autism, and Opioid Addiction as Natural and Induced Disorders of the Endogenous Opioid Hormonal System

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Abstract: *Introduction*: Because of their circulation through the blood, the multiplicity of receptor sites, and the diversity of functions, opioids may most accurately be designated as a hormone. Opioids modulate the intensity of pain. In mammals, the opioid system has been modified to modulate social interactions as well (Panksepp and Watt, 2011). *Methods*: Over 10,000 patient encounters were observed on a neuropsychoanalytic addiction medicine service. Cold pressor times (CPT) were recorded before and after stimulation of the opioid system with low-dose naltrexone (LDN) for patients after opioid detoxification and for fibromyalgia patients. *Results*: Patients maintained on opioids relate autistically. The cold, unrelated nature of their human interactions was reversed by detoxification from opioids. Fibromyalgia patients have difficulty participating in human relationships, as if they lack an ability to respond interpersonally, as do post-detoxification patients. LDN improved pain tolerance as shown by a significant increase on CPT for post detoxification patients from 16 seconds to 55 seconds and in fibromyalgia patients from 21 seconds to 42 seconds, and improved relatedness. The correlation of opioid prescribing increasing over time and autism prevalence increasing over time is highly significant. *Conclusions*: 1. Opioid-maintained patients relate autistically. 2. Autism is a hyperopioidergic disorder. 3. Fibromylagia is a hypoopioidergic disorder. 4. Low opioid tone caused by opioid maintenance or fibromyalgia can usually be reversed with low-dose naltrexone. 5. The increase in the incidence of autism may have been caused by the increase in use of opioids for analgesia during childbirth.
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Neuropsychoanalysis is a 21st century interdisciplinary field that uses both neuroscience to inform close observation of patients, and psychoanalytic thinking to inform nomothetic observations of brain function (Solms and Turnbull, 2011). A neuropsychoanalytic addiction medicine service was created at the State University of New York (SUNY) Upstate Medical University in 2009. A pain service was embedded in this addiction medicine service in order to evaluate patients' pain complaints, since these complaints are a major driving force and justification for opioid prescribing (Okie, 2010). The psychoanalytic tradition of facilitating the patient's description of their inner states -- the polar opposite of the cognitive behavioral method of teaching the patient recovery skills -- has gradual deepened our understanding of the endogenous opioid system.

Since its inception in 2009 the addiction medicine service has had more than 10,000 encounters, including 4,504 outpatient visits in 2013. Approximately half of the patients admitted to the addiction medicine service have opioid use disorders. (For a longer description of the service, see Johnson and Faraone, 2013.) The addiction medicine portion of the service is staffed by psychiatry residents and medical students while the pain service adds neurology residents and pain fellows. Addiction medicine medical students and psychiatry residents perform initial evaluations, extended evalua-

tions in a psychoanalytic therapy context, and University Hospital consultations, all overseen by the first author of this article. Patients are required to bring a "sober support person" to the initial evaluation. This person is most commonly a romantic partner, family member, or friend. The support person is present for the entirety of the initial evaluation and treatment planning session, and often returns episodically during the extended evaluation period. Clinical observations are discussed in an academic setting. The first author sees all patients on every visit. The purpose of this communication is to describe the observations, and the model of the endogenous opioid system that has been constructed using our observations.

I. The Endogenous Opioid Hormonal System

Opioids are produced by a number of sites, including the adrenal gland, the pituitary gland, and the hypothalamus. There are a plethora of targets for these opioids located throughout the body as enumerated in Table 1 (Snyder, 2004; Sehgal *et al*., 2011; Laux-Biehlmann *et al*., 2013). Heretofore opioids have been characterized as a "neurotransmitter peptide" (Snyder, 2004) or "neuropeptide." By definition, a hormone is a substance produced by one tissue and conveyed by way of the bloodstream to another tissue to effect physiological activity. Given this definition, endogenous morphine (unfortunately contracted to the Greek-sounding term "endorphin") and other opioid peptides such as enkephalins and dynorphin should be classified as constituents of a larger opioid hormonal system. Like any other hormonal system, it is susceptible to both natural and iatrogenic diseases.

Table 1. Targets of the Endogenous Opioid System.

1. Gastrointestinal System • Gut
2. Blood • Monocytes • B-Lymphocytes • T-Lymphocytes • Mast Cells
3. Integumentary System • Keratinocytes
4. Musculoskeletal System • Synovium
5. Peripheral Nervous System • Peripheral Nerve Fibers • Dorsal Root Ganglia
6. Central Nervous System • Periaqueductal Grey • Medial Thalamus • Hippocampus • Striatum • Locus Ceruleus • Substantial Gelatinosa of the Spinal Cord • Substantial Gelatinosa of the Brainstem
References: Snyder, 2004; Sehgal *et al*., 2011; Laux-Biehlmann *et al*., 2013.

Hypothesis 1 -- The Endogenous Opioid System is a Hormonal System that Regulates Both Pain and Relatedness

Opioid modulation of pain has been adapted by social animals to also modulate relatedness (Stein *et al*., 2007). Animal studies show that activation of mu-opioid receptors is essential for social attachment (Burkett *et al*., 2011) and that mu-opioid receptors in the nucleus accumbens mediate social behavior (Trezza *et al*., 2011). In humans, variants of the mu-opioid receptor gene will affect an individual's social hedonic capacity (Troissi *et al*., 2011) and sensitivity to social rejection (Way *et al*., 2009). Opioids generate a pleasant feeling that both promotes and regulates the sensation of relatedness. Low opioid tone is associated with low levels of human relatedness and painful social dysphoria (Trezza *et al*., 2011).

We suggest that low opioid tone prompts urges to make human contact in healthy persons. For example, after a night alone, one might be happy to see one's partner, children, and/or colleagues. Antithetically, after a hectic day with one's colleagues, coming home to one's partner and children, after family time and child bedtime, it might feel wonderful to sit quietly alone with a book to counteract the dysphoria of opioid overstimulation. The region labeled "healthy functioning" in Figure 1 is meant to indicate the degree of opioid tone maintained by healthy individuals, as modulated through social interactions.

Patients on opioid maintenance relate autistically. They often avoid making eye contact (gaze avoidance). Once detoxified these patients become related again. Some report having felt apathetic about robbing family members to buy drugs, as if there were no inner feelings of being related.

Given the aforementioned evidence, we hypothesize that fibromyalgia, opioid post-acute withdrawal syndrome, and autism are diseases of hormonal production, similar to those disease states seen in peripheral glands such as the thyroid. A major difference between peripheral hormones and opioids is that the latter are tightly regulated by a series

of opposing and modulating neurotransmitters and neuropeptides including, but not limited to, glutamate, corticotrophin releasing factor, substance P, and dynorphin (Koob and Volkow, 2010). These key regulatory differences greatly influence treatment approaches for diseases of the opioid system.

Unlike treatments for peripheral glandular disorders in which hormone replacement is a mainstay of therapy, simply replacing opioids does not work for disorders in which opioid tone is low, as appears to be the case in opioid post-acute withdrawal syndrome and fibromyalgia. A likely explanation for this observation is provided by the opponent process theory, which suggests that, in the central nervous system, opioid-induced hedonic states trigger negative hedonic responses that grow larger with repeated exposure to opioids (Koob and Volkow, 2010). Opioid induced up-regulation of the drivers of pain, anxiety, and depression begin early on in drug use, forming one of the major motivations for the compulsive nature of drug use. This process is consistent with observations of opioid induced hyperalgesia (OIH) (Chu *et al*., 2008). With greater opioid exposure, baseline pain increases.

Naltrexone is the ideal drug for the modulation of opioid tone, because of its activity as a mu-opioid receptor antagonist. At high doses, its blockade of opioid receptors reduces opioid tone while at low doses naltrexone enhances both opioid receptor expression as well as serum met-enkephalin and beta-endorphin levels (Brown and Panksepp, 2009). Based on these findings, naltrexone should be efficacious for treating disorders of both increased and decreased opioid tone.

II. A Novel Approach to Opioid Addiction

Johnson (2001; 2010) used neuropsychoanalytic observations in conjunction with neuroscientific models (Koob and Volkow, 2010) to explain reasons for opioid detoxification failure and the subsequent relapse to opioids. If opioids positively modulate the effects of interpersonal relationships, then individuals should be susceptible to opioid addiction if they lack the ability to relate interpersonally with others. Therefore, the euphoria described as a result of exogenous opioid administration would be analogous to the positive emotions that are generated from normal interpersonal interactions. In other words opioids serve as a "person in a pill." As one patient described it, "You know that feeling you get when you are in love? That's how I feel on oxycodone." When detoxification has stripped patients of opioids,

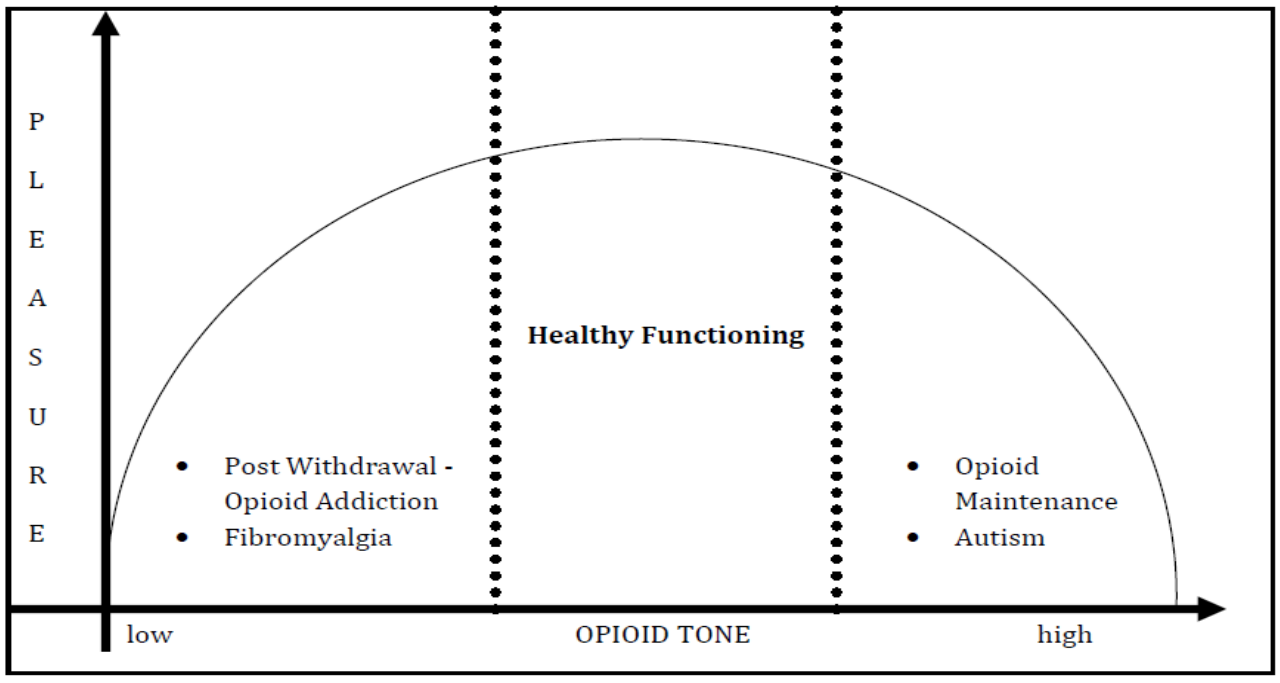

Figure 1. The hypothesized "inverse U" relationship of pleasure and opioid tone in central nervous system subcortical pathways. The left side of the x-axis corresponds with low opioid tone, associated with post acute withdrawal syndrome and opioid induced hyperalgesia (OIH) after opioid withdrawal and with fibromyalgia. The right side of the x-axis corresponds with high opioid tone, associated with patients maintained on opioid drugs and with autism. Pleasure is at its peak when regulated by human interactions in the band labeled "healthy functioning."

they often feel as if they are traumatized by the emotions provoked by renewed relatedness. The first reason for relapse is the rush of anxiety accompanying feelings associated with the cessation of opioid use. This sudden availability of emotions was the impetus for having daily, hour-long, psychotherapy sessions during the week of opioid withdrawal. Once withdrawal has stopped, these sessions are decreased to twice weekly until the patient ultimately enters a longer-term process of recovery. In some cases patients begin active participation in 12-step recovery. Some patients are additionally referred to a long-term psychoanalytic therapist. They may be discharged from treatment because their recovery seems to be progressing without additional intervention.

A second cause for relapse was considered to be the perpetual craving for opioids, which is augmented by the use of other drugs, especially nicotine (Stuyt, 1997). As a result, nicotine cessation has become a central focus of opioid cessation treatment. Drug dreams (Johnson, 2001; Colace, 2014) have commonly been analyzed, providing important information about drug craving by way of dream interpretation. In this neuropsychoanalytic light, drug dreams are viewed as the consequence of altering the dopaminergic drive pathway by taking addictive drugs, a pathway originally built into humans so that we pursue food or sex. This altered drive pathway creates an unreasonable urge to seek opioids (Johnson, 2013).

A third reason for relapse was deemed to be the protraction of withdrawal symptoms (Koob and Volkow, 2010). The cold pressor test (CPT) uses an ice-water bath with a circulator pump. The test subject submerges their forearm into the ice-water. The duration of tolerated submersion is used as a measure of pain tolerance (Pud *et al*., 2006). Results of normal subjects measured on our service are similar to the findings of other studies (Walsh *et al*., 1989), with a time under 35 seconds being below the 95th percentile. The average CPT for normal subjects is 102 seconds. Several reports indicate that post-detoxification CPT are persistently shortened (Triester *et al*., 2012; Ren *et al*., 2009), suggesting that opioid withdrawal is often persistent. In fact, it is unclear if opioid induced hyperalgesia/protracted withdrawal ever completely ends. Though most would like to assume that suppressing the endogenous opioid system with exogenous hormone is always reversible, no studies have explored whether or not this is true.

Using the idea proposed by Brown and Panksepp (2009) about stimulating the endogenous opioid system, the first author began administering low-dose naltrexone (LDN) to post detoxification patients, in hopes of stimulating the increase of endogenous opioid tone, which had presumably been degraded via the administration of exogenous hormone. With the Institutional Review Board approval, outcomes of a case series are reported below.

The study used 41 subjects, 21 women and 20 men, with an average age of 49 (Table 2). Patients were included if there was a baseline CPT and a repeat CPT at 2 weeks or more after the beginning of LDN administration. If both criteria were met, then the best and worst results were tabulated. The follow-up time varied from two weeks to six months, owing to the clinical nature of the setting and study population. We provide the "Worst CPT" value in order to demonstrate that there was not a random increase in measured values; rather, the improvement in pain tolerance tended to be persistent. The observed increase in CPT findings subsequent to LDN treatment was statistically significant.

Hypothesis 2 -- Neuropsychoanalytic Therapy Including LDN Enhances Outcomes of Opioid Addiction Treatment by Addressing Key Aspects of the Disease Including Persistent Low Opioid Tone

The increase in CPT from 16 seconds, for hyperalgesic patients, to 55 seconds suggests the possibility that endogenous opioid tone has been augmented by the transient blockade of opioid receptors causing a rebound of improved function (Brown and Panksepp, 2009). On occasion patients describe an experience of feeling relaxation and diminished pain that occurs approximately one hour after LDN administration, as if they can feel the endogenous morphine rebound. The standard dose of naltrexone for alcohol use disorders is

Table 2. Improvement in Pain Tolerance Before and After Stimulation with Low-dose Naltrexone.

Population	Baseline CPT	Best	Worst	P Value
All Subjects	15.75 (9.10)	55.38 (49.24)	48.62 (51.27)	<0.0001
Men	19.05 (8.42)	59.5 (55.94)	56.6 (57.62)	<0.0001
Women	12.62 (8.79)	53.76 (43.14)	43.00(45.28)	<0.0001

Note: Standard deviation values are shown in parenthesis.

100 mg (Anton *et al*., 2006). Initially, the first dose used in the study population was 1 mg. Many patients experienced a worsening of opioid withdrawal symptoms with first dose administration. Therefore the initial dose was reduced to 0.1 mg, mostly abating this phenomenon. Occasionally patients still describe opioid withdrawal symptoms provoked by 0.1 mg of naltrexone. After the initial dose of 0.1 mg, the LDN dosage is gradually increased to 4.5 mg over a period of three weeks. If a patient still reports withdrawal symptoms related to LDN administration, their dosage is escalated at a slower rate and over a longer period of time.

The aforementioned precipitation of withdrawal symptoms in response to miniscule doses of naltrexone in our previously opioid-maintained patients is worrisome. This observation suggests that chronic opioid administration, whether by a physician or by a heroin dealer, is no different in terms of adverse response to naltrexone. In other words, both heroin and prescription opioid medications degrade the endogenous opioid system. Since this system is crucial to the modulation of pain, opioid maintenance for patients with chronic pain may cause a persistent exacerbation of the patient's pain -- whether the opioids are continued or not.

Using this neuropsychoanalytic approach to opioid addiction treatment has yielded unusually good outcomes, including a 92% completion rate for outpatient opioid detoxification (Johnson and Faraone, 2013). We hypothesize that opioid tone is restored towards normal by the intense human contact of a psychoanalytic therapy in conjunction with the administration of LDN.

III. Fibromyalgia

The presence of a pain service embedded in our addiction medicine service has resulted in the referral of fibromyalgia patients who were not necessarily addicted to opioids. The diagnosis of fibromyalgia was established by careful evaluation, including physical examination for trigger points, with at least 11/18 present in about 90% of diagnosed patients. We found surprising congruencies between the symptoms experienced during opioid withdrawal and fibromyalgia. As illustrated in Table 3, the clinical presentations for fibromyalgia and opioid withdrawal are strikingly similar -- that is, fibromyalgia patients present as if they were in perpetual opioid withdrawal.

Opioid addicted patients frequently have short CPT as is almost always the case with fibromyalgia patients. Given the positive response of our opioid addicted patients to LDN, we decided to administer LDN to our fibromyalgia patients. This approach has also been used by the Stanford pain group (Younger *et al*., 2013), although they expressly state that the endogenous opioid system is not involved in the ameliorative process (Younger *et al*., 2009). They showed a significant response to a fixed dose of 4.5 mg of naltrexone. Our approach differs from that of the Stanford pain group in that it involves tailoring the dose to each patient's individual response. Furthermore, our method differed in that the naltrexone was administered twice daily because patients reported that a second daily dose helped more than once a day dosing.

Table 3. Congruity of Opioid Withdrawal and Fibromyalgia Symptoms, As If Fibromyalgia Patients Are in Perpetual Opioid Withdrawal.

Symptom	Opioid Withdrawal	Fibromyalgia
Feels cold	Common	Common
Diarrhea	Common	Common, often diagnosed with comorbid "irritable bowel syndrome"
Restless legs	Common	Common
Depression	Common	Common
Intolerable anxiety	Common	Common
Non-restorative sleep	Common	Common
Fatigue	Common	Common, often diagnosed as "chronic fatigue syndrome"
Generalized pain	Common	Common
Vocational dysfunction	Common	Common
Diaphoresis	Common	Common
Trouble thinking	Common	Common, often described as "fibrofog"

The results for the response of our first patient were previously published and described his response over a six-month period (Ramanathan *et al*., 2012). Over this time, his CPT improved from 7 seconds to about 60 seconds. Our larger case series is shown below and included 19 women and 1 man (Table 4). The average age of our study's participants was 44 years. The difference between the baseline and the follow-up CPTs was statistically significant (p=0.0036, standard deviation in parenthesis).

Hypothesis 3 -- Fibromyalgia Is an Autoimmune Disease of the Endogenous Opioid System

Based on our findings and fibromyalgia's observed preponderance for women, we hypothesize that fibromyalgia is an autoimmune disease targeting the endogenous opioid system. The female:male ratio is 3:1, which is the exact ratio seen in other autoimmune diseases. Patients who are able to respond to LDN may have a low-functioning opioid system that can be stimulated by a transient blockade of the opioid receptors. This stimulation presumably causes an increase in opioid tone allowing the system to return to a level more closely resembling the range of "healthy functioning" illustrated in Figure 1. We hypothesize that non-responders have had their opioid system ravaged to such a degree that they have little left to stimulate. In our study, 4 of the 20 patients showed little change in CPT. These include 3 patients whose CPT actually worsened with LDN.

IV. Autism

Autism is a neurodevelopmental disorder characterized by deficient social interactions, poor communication skills, and repetitive, stereotyped behaviors. To date, there are no effective medical interventions for these core deficits (American Psychiatric Association, 2013; World Health Organization 1992; 1993). Modern pharmacotherapeutic approaches aim at eliminating disruptive behaviors (e.g., atypical antipsychotics) or treating comorbid disorders (e.g., stimulants for ADHD). Current hypotheses about autism's pathophysiology have focused on an explaining the diverse nature of autism's symptomatology. Concomitant phenomena including constipation, pain insensitivity, and immune changes have led some to hypothesize that autism is a disease of heightened opioid tone, given that the gut, pain system, and immune cells are all known to possess opioid receptors. The correlation of low pain sensitivity, high endogenous opioids levels, and autistic behaviors was first described by Panksepp (1979) and has since been associated with elevated beta-endorphin levels. The 1994 Leboyer *et al*. study describes findings for beta-endorphin levels in patients with infantile autism as well as for normal comparison subjects. The patients with infantile autism possessed plasma beta-endorphin levels ranging from approximately 7 to 210 pg/mL, while the control subjects possessed beta-endorphin levels ranging from approximately 0 to 20 pg/mL. Of the subjects with infantile autism, 82% possessed beta-endorphin levels exceeding those of their normal counterparts. It is of interest to note that elevated beta-endorphin levels have since been found amongst non-autistic relatives of autistic patients, suggesting a familial mode of transmission (Leboyer *et al*., 1999).

Table 4. Results of Neuropsychoanalytic Treatment of Fibromyalgia.

Baseline CPT	Best CPT
20.75 (18.89)	42.20 (37.82)

As noted previously, the opioid system plays a crucial role in social interactions among humans. Based on these observations and the notion that human contact positively modulated opioid tone, a disorder of abnormally heightened opioid tone would result in dysphoria exacerbated by interactions, causing children to minimize human contact. In order to reduce such contact, these children would avoid looking at others, avoid learning language, and, perhaps, even perform repetitive behaviors as an attempt to keep others away. Conceptualizing autism as a disorder in which high levels of endogenous opioid expression lead to its manifestations would provide physicians with a paradigmatic framework within which they could design and implement treatments.

Naltrexone has been shown to produce a clinically significant reduction in the serious and life-threatening behavior of self-injury which occurs as a result of a discorded endogenous opioid system (Sandman and Kemp, 2011; Sandman, 2009). Researchers of self-injurious behaviors (often associated with autism) have implicated the opioid system, and have tested the possibility that these behaviors were driven by a wish for an opioid high.

Our hypothesis is the diametrically opposed to the view that self injurious behaviors are undertaken to increase opioid tone. Rather, we propose that these self-injurious behaviors are driven by excessive opioid tone -- with the injuries serving to upregulate pain sensors in order to balance uncomfortable opioid tone. Rather than achieving an opioid high, we believe that these behaviors are an attempt by the patient to achieve an opioid low. Pilot work on the use of naltrexone for autism has

been carried out by Panksepp and collaborators (Lensing *et al*., 1995). These studies show that blocking the opioid system with naltrexone at high doses of 0.5, 1.0, and 2.0 mg/kg reverse the autistic behaviors and gaze aversion. To date, 0.5 mg/kg appears to be the best dose, and is equivalent to 35 mg for a 70 kg adult. Unfortunately, these small pilot studies have not been followed up with larger studies.

Despite these favorable, albeit limited, results, prior studies investigating the use of naltrexone for autism have not been uniformly positive. The same is true for studies of pain sensitivity and naltrexone (Nader *et al*., 2004). These results may be attributed to the heterogeneity of autism, leading to our speculation that only a subset of autistic patients -- those identified by elevated beta-endorphin levels -- will respond to naltrexone treatment. A comprehensive review of all articles describing and/or evaluating the efficacy of naltrexone in pediatric patients with autism uncovered a single case study consisting of ten children treated with naltrexone in which beta-endorphin levels were measured (Cazullo *et al*., 1999). Of the ten children, seven were considered responders as they had lower beta-endorphin levels during the three month period during which they were treated with naltrexone. This reduction in beta-endorphin levels reduced symptoms on behavioral scales ($p=0.0001$), improved socialization, and reduced behavioral problems. The three nonresponders had persistently elevated beta-endorphin. As a consequence of our hypothesis that opioids act as hormones, we suggest that autism treatment should focus on reducing serum beta-endorphin levels to the normal range so that the internal stimulus of opioid tone can more effectively modulate human interactions.

Patients on opioid maintenance are oddly unrelated. This can take the form of a cold "dope fiend" demeanor. The person is present, talks to you, but is nonetheless unrelated. The experience is of speaking with a person who is not really there. Support persons of opioid-maintained patients often note an enhancement in relatedness that occurs with detoxification. It is not uncommon to hear a support person to relate a story such as, "I didn't bother spending time with her, because she was just zonked all day. Suddenly I have the woman I married back!" Or, "Jennifer called me from the supermarket (after detoxification) to ask if I wanted anything. She hadn't called me in years!" This change in relatedness is dramatically apparent to all treaters. The similarity between the unrelatedness of opioid maintenance and autism was discussed in the 1970s (Kalat, 1978). This observation of an important side effect appears to have been lost over time as an aspect of treating patients with opioid maintenance, whether for pain or opioid addiction.

Hypothesis 4 -- Autism May Be Treatable with High Dose Naltrexone

Though there are an abundance of theories as to the cause of autism, Panksepp's idea that autism is related to opioid overactivity is supported by our observations of the interactions of opioid maintained patients and their responses to detoxification. While opioid overactivity that results from the exogenous administration of opioids is reversed by detoxification, autistic opioid overactivity can be blocked with high-dose naltrexone (HDN). Although trials of various doses of naltrexone have been performed by various authors (Roy *et al*., 2014) including Panksepp and colleagues (Leboyer *et al*., 1992), and have shown some positive results, use of monitoring of beta-endorphin levels to adjust dose of HDN is absent from the research literature of autism. We suspect that just as decreasing opioid tone by detoxifying opioid-maintained patients improves relatedness, blocking beta-endorphin back to the normal range would ameliorate the symptoms of autism.

V. The Pervasiveness of Autism Spectrum Disorders

Autism spectrum disorders are characterized by impaired interpersonal behaviors and/or communication that can be observed as early as six months of age (Shic *et al*., 2014). The endocrine system has been implicated in the etiology of autism by two key lines of evidence. First, males are four times as likely as females to be diagnosed with autism. Second, the adrenal, gonadal, and thyroid hormones all play an important role in neurodevelopment (Braun *et al*., 2014). Braun *et al*. went on to hypothesize that in-utero environmental exposures may increase the risk of autism. If the opioid system is in fact a hormonal system, it is conceivable that opioid administration during childbirth may alter the tone of this system. We propose that the pain of childbirth provokes a natural spike in maternal beta-endorphin levels which in turn sets the tone of the opioid system in the newborn. By enhancing the level of opioid tone at birth with exogenous hormone (opioids), the level of fetal opioid tone would also be enhanced. Intriguingly, Bauer and Kriebel (2013) have proposed that exposure to acetaminophen may be responsible for the link between analgesics and autism. After examining their line of reasoning, we believe that it is the opioid analgesic substances -- present with acetaminophen in many formulations -- which is responsible for the manipulation of the opioid system, ultimately resulting in autism.

According to the Hong (2010) review of the history of neuraxial labor analgesia, in 1979 there was a "call to arms" regarding the use of opioids for epidural labor

anesthesia. Though combined spinal-epidural analgesia became more common in the 1980s, it did not enjoy widespread popularity until the 1990s. As this use of analgesia became more common, the philosophy of when to provide opioids for analgesia shifted towards use earlier in labor, with Wong *et al*. (2009) providing evidence in a large case series of nulliparous women of the desirability of starting opioids earlier in labor, before the cervix had dilated past 5 centimeters.

Opioids are transmitted from maternal to fetal circulation as evidenced by the possibility of neonatal respiratory depression as an important potential complication of provision of opioids during labor (Ackerman and Dresner, 2009). More specifically, cord blood beta-endorphin and maternal plasma beta-endorphin appear to co-vary during labor. Chan *et al*. (1993) explained this observation as, "Labors that are stressful for the mother tend to be stressful for the fetus and vice versa."

According to Clinical Management Guidelines for Obstetrician-Gynecologists (Goetzl, 2002), "Labor results in severe pain for many women. There is no other circumstance in which it is considered acceptable for a person to experience untreated severe pain, amenable to safe intervention, while under a physician's care. In the absence of a medical contraindication, maternal request is a sufficient medical indication for pain relief during labor…" The clinical guidelines list meperidine, fentanyl, nalbuphine, butorphanol, and morphine as parenteral agents for labor pain. Over the period that autism's incidence has increased dramatically, there has been a concomitant increase in the use of opioid medications by physicians (Volkow, 2011). Why has the incidence of autism increased so dramatically over the years? Our hypothesis is that the increase in autism is the result of a change in the culture of obstetric analgesia use. Opioid administration during labor has gone from unusual to ubiquitous.

Table 5. Changes in U.S. Autism Rates.

Year	CDC Prevalence of Autism
1975	2
1985	4
1995	20
2001	40
2004	60
2007	67
2008	113
2010	147

Note: Results are in multiples of 10,000. Sources: Duchan and Patel, 2012; http://www.cdc.gov/ncbddd/autism/data.html (accessed 4/26/2014.

Hypothesis 5 -- The Increasing Prevalence of Autism Is Caused by the Increasing Administration of Opioids During Childbirth

There is now a substantial literature on opioid induced hyperalgesia (OIH) that shows that a single administration of opioid, if provided for sufficient time, will induce hyperalgesia, representing a resetting of opioid system functioning (Angst *et al*., 2010). Brimstead *et al*. (1985) has established that there is a natural spike in maternal and, most probably, fetal beta-endorphin during labor. This study showed the beta-endorphin levels for three groups of pregnant subjects measured at 38 weeks gestation, at labor, and at 4 days post partum. The first group of subjects received no analgesia during labor and had an average corresponding intrapartum beta-endorphin level of approximately 45 *f*mol/mL. The second group received epidural intrapartum analgesia and had a corresponding beta-endorphin level of approximately 18 *f*mol/mL. The third group was given an opioid analgesic (pethidine) intrapartum and had an average corresponding beta-endorphin level of approximately 70 *f*mol/mL. In other words, concomitant administration of an opioid analgesic during labor results in a supraphysiologic serum beta-endorphin spike in the laboring mother and, most probably, the child being born.

We hypothesize that administration of opioids during labor interferes with the natural fetal opioid balance. We believe that there is a genetic component which makes certain individuals more susceptible to interference from intrapartum opioid administration. In these susceptible individuals opioid administration during labor somehow resets their opioid system, causing it to function at an abnormally elevated level. This two-factor event, genetic vulnerability and environmental insult, causes some newborns to develop an overactive endogenous opioid system, which we hypothesize produces autism. This early hormonal disorder is not initially apparent, but becomes readily apparent during later development when parents begin to observe that infants avoid human interactions that provoke increased endogenous opioid tone which is dysphoric for the autistic child.

If opioid medications administration during labor were correlated with the development of autism in the children born under this medication regimen, we would have the "medical contraindication"

described in the clinical management guidelines. Knowledge of this complication of opioid administration during labor would alter practice and potentially reduce the incidence of autism. To our knowledge, no one has previously suggested this hypothesis, as it comes out of our overarching conceptualization of disorders of the endogenous opioid hormonal system and our clinical observations involving both patients addicted to opioids and those suffering from chronic pain.

Conclusive evidence for this hypothesis would require a randomized, double blind prospective study of opioids or another analgesic given for the pain of labor. However, suggestive evidence is provided in Table 5, Table 6, and Figure 2.

Conclusion

The endogenous opioid hormonal system is an integral driver for human health including the human need for relatedness. When this system is disrupted, illness may ensue. Various aspects of medical practice may be affected by our model of this system including fibromyalgia, pain management, addiction treatment, autism treatment, and obstetric practice. Although there are cells in the adrenal glands that produce endogenous opioids, we see the central hypothalamic and pituitary opioid producing cells as the most important. These cells communicate with other central nervous system components in a way that produces a fragile ecology of drivers and inhibitors of pain, anxiety, and depression. If supported, our hypotheses might change the diagnostic and treatment approach to a wide range of medical and psychiatric disorders.

Provision of exogenous opioid hormones may have significant long-term, or even permanent, consequences that are not currently accounted for in medical practice. The linkage between opioid maintenance and autism allows medical practitioners to appreciate a side effect of opioid administration that usually escapes notice. Opioids generally supplant the need for relatedness (Pally, 2000). Chronic use may lead to avoidance of social interactions. In addition, the effectiveness of long-term opioid therapy for chronic pain is not well supported in the literature; use of the drugs may not lead to pain relief and improved functional status, and it is often accompanied by adverse side effects (Manchikanti *et al*., 2011).

These hypotheses may help practitioners to better understand the results of prescribing opioids. Patients experiencing consistently low endogenous opioid tone may find that opioid prescriptions immediately give them gratifying opioid tone, creating a wish to secure more prescriptions. The concept of the opioid system as a modulator of human relatedness would move physicians to use more caution when prescribing opioids for they would understand that they would be potentially providing the patient with a powerful psychoactive drug.

The central hypothesis of this study is that the endogenous opioid system is a fragile, malleable brain system that should be altered by administration of opioid medications only with full knowledge of the consequences. Should these hypotheses be confirmed, the results could

Table 6. Opioid Prescriptions Issued in the United States by Year.

Year	Millions of Opioid Prescriptions -- from Volkow, 2011 (Autism Rate)
1991	76 (estimate 10)
1992	78
1993	80
1994	86
1995	91 (20)
1996	96
1997	97
1998	109
1999	120
2000	131
2001	139 (40)
2002	144
2003	151
2004	158 (60)
2005	169
2006	180
2007	192 (67)
2008	201
2009	202
2010	210 (147)

Note: A paired t test of the above six points showed a correlation, p=0.0003.

lead to a reduction in the administration of exogenous opioid administration by physicians, preventing new disease, while providing clinically relevant solutions to widespread, previously devastating disorders of this system.

The conceptual model of an opioid hormonal system provides heuristic value in making predictions that could be empirically validated:

- Vulnerability to opioid addiction would be predicted by the ability of the opioid-naive subject to make human relationships. Well-related persons would be functioning in the normal range and find exogenous opioid administration aversive. Poorly related persons would find exogenous opioid administration a welcome relief from the emotional pain of low opioid tone. These would be the persons at risk for addiction.

- Reversing physical dependency on opioids would be different for different populations. Well-related persons would find detoxification a relief whereas poorly related persons would once again be exposed to the pain of unrelatedness. We have provided some limited support for this hypothesis (Johnson and Faraone, 2013) and suggested that we have given evidence that the diagnostic criteria for opioid use disorder should be modified. Well related persons who experience tolerance, withdrawal, and inability to stop opioid medications may only be afraid of the withdrawal syndrome rather than being truly addicted.

- Low-dose naltrexone would be an ameliorative agent for fibromyalgia if sufficient opioid function remained after an autoimmune attack on the system. Stimulating the remaining opioidergic cells or receptor systems might return opioid tone towards the normal range. This concept could be tested using a double blind randomized study. Beta-endorphin levels might be followed to see if they increased, and if the increase was correlated with remission of fibromyalgia symptoms.

- Low-dose naltrexone may improve the prognosis of opioid addicted individuals after detoxification. The model of relapse, that emotional issues, ventral tegmental dopaminergic SEEKING of opioids, and post acute withdrawal fatigue, pain, anxiety, insomnia are the three drivers of relapse, provides a model that could be tested by comparing the neuropsychoanalytic treatment approach to other treatment approaches such as cognitive behavioral therapy or opioid maintenance.

- A blocking dose of naltrexone may be an effective treatment of autism. This idea was originated by Panksepp (1979) and expounded upon by Leboyer *et al*. (1992), but seems to have been largely ignored. Similar to the approach to opioid addiction, medication treatment alone would likely not be sufficient without an intense psychotherapy base for the treatment. The model predicts that patients with autism would have an

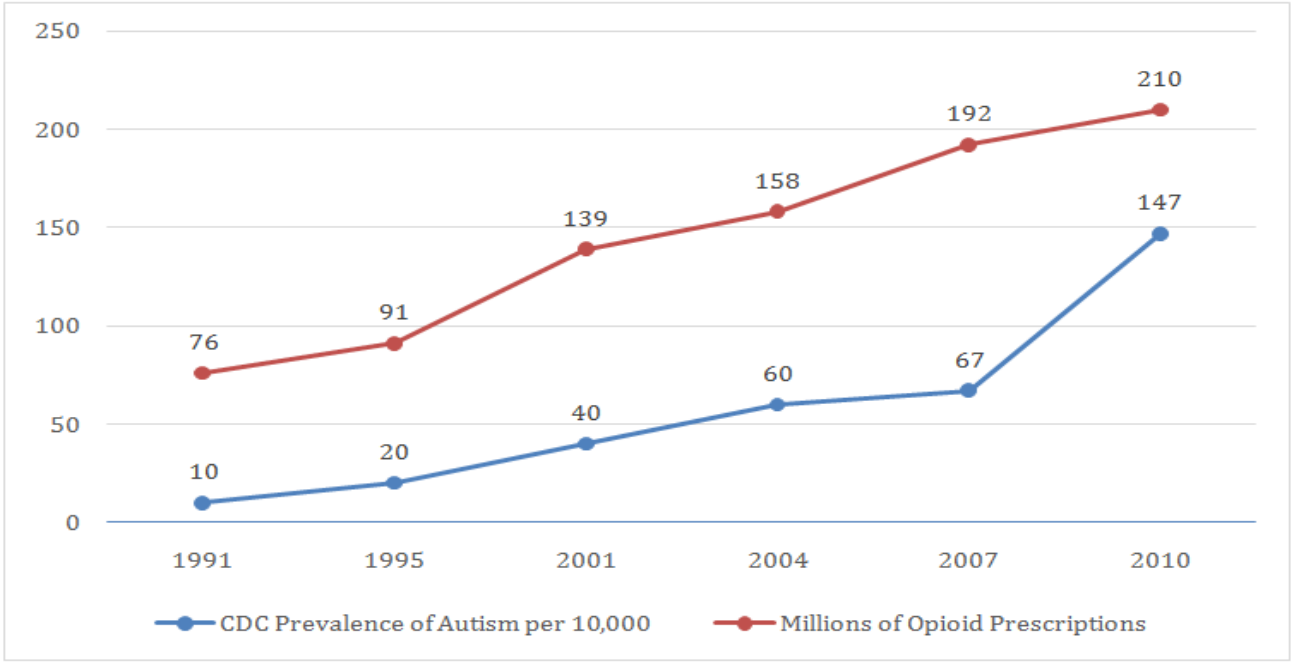

Figure 2. Autism rate and opioid prescription correlation shown graphically.

underdeveloped capacity for relatedness due to being born with high opioid tone that made human contact aversive. New exposure to human emotions caused by amelioration of the biological correction by naltrexone would have to be a central focus of psychotherapy care.

- Administration of opioid medications during childbirth has gone from unusual to strongly recommended between the time that autism was a rare disorder, and now, when it afflicts more than 1% of children in the United States. The hypothesis that autism is caused by a genetic predisposition triggered by administration of exogenous opioid hormone/medication at birth can also be operationalized and tested.

Disclosure

The authors report no conflicts of interest.

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